IV. REMARKS/ARGUMENTS

A. Status of Claims

Claims 38, 39 and 46-50 are currently pending. Claims 1-37 and 40-45 were previously cancelled.

B. Rejection under 35 U.S.C. 103 (a) over Baker et al. and Penning et al.

In the Office Action, the Examiner rejected claims 38-39, 46-48 and 50 under 35 U.S.C 103 (a) over US 4,569,937 (hereinafter "Baker et al.") and Penning et al., J. Med. Chem. Vol. 40(9) (April 1997) pp. 1347-1365. The Examiner stated that "one of ordinary skill in the art would have been motivated to substitute celecoxib for ibuprofen in the Baker reference compositions in light of the Penning reference teaching that celecoxib is analgesically potent with less side effects (e.g. as compared to NSAIDS e.g ibuprofen)...".

This rejection is traversed. Applicants respectfully submit that one skilled in the art would not be motivated to substitute the ibuprofen of the formulations of Baker et al. with celecoxib in view of Penning et al. In the Office Action, the Examiner supports his arguments, in part, on the assumption that Baker et al. point to a broad class of NSAID's which function to treat inflammatory pain. (see page 3, lines 11-19 of the Office Action). However, Applicants have reviewed Baker et al. and have found no support for this assumption. Columns 1 –2, cited to by the Examiner, only mention the acronym 'NSAID' twice at column 1, lines 21 and 23, and that is in a discussion of prior art; it is not a teaching of Baker et al. If the Examiner is aware of support in Baker et al. for the notion that Baker et al. points to a broad class of NSAIDs for use in their invention, Applicants would appreciate the Examiner pointing out the appropriate passage.

Based on Applicants review of Baker et al., it appears that Baker et al. rejected all NSAIDs in their invention *except* ibuprofen. The purported invention and teachings of Baker et

al. are limited to the combination of a narcotic analgesic and ibuprofen. The Examiner is respectfully directed to column 1, lines 6 - 9 of Baker et al. which states as follows:

> *This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*
> (Emphasis Added)

The Examiner is also directed to column 2, lines 11-15 of Baker et al. which states as follows:

> *According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*
> (Emphasis Added)

The following additional passages from Baker et al. are also limited to a combination of narcotic analgesics and ibuprofen:

Column/Lines	**Text**
Title:	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Abstract:	ABSTRACT Pharmaceutical compositions of narcotic analgesics and ibuprofen . . .
Figure 1	ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN . . .
Col. 1, line 1 & 2	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Col. 2, lines 20-24	. . . synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof . . .
Col. 2, line 34 & 35	. . . various dose ratios of oxycodone and ibuprofen.
Col. 2, lines 64 & 65	In a composition of the invention, oxycodone and ibuprofen are combined . . .
Col. 3, lines 23 & 24	. . . unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen . . .
Col. 3, lines 53-56	. . . the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen.

Column/Lines	Text
Col. 4, lines 24-29	Example 1 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 4, lines 36-42	Example 2 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 300.0
Col. 4, lines 48-55	Example 3 Oxycodone/Ibuprofen Tablets Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 4, lines 60-66	Example 4 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 8-14	Example 5 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 300.00
Col. 5, lines 20-26	Example 6 Oxycodone/Ibuprofen Capsules Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 5, lines 33-39	Example 7 Oxycodone/Ibuprofen Tablets Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 45-51	Example 8 Oxymorphone/Ibuprofen Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 5, lines 58-63	Example 9 Oxymorphone/Ibuprofen Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 1-7	Example 10 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 60.0

Column/Lines	Text
Col. 6, lines 13-19	Example 11 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 6, lines 25-31	Example 12 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 38-43	Example 13 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 6, lines 49-55	Example 14 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 6, lines 61-66	Example 15 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 9-14	Example 16 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 7, lines 21-27	Example 17 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 7, lines 33-39	Example 18 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 46-51	Example 19 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 7, lines 57-63	Example 20 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 300.0

Column/Lines	Text
Col. 8, lines 1-7	Example 21 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 13-19	Example 22 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 8, lines 26-31	Example 23 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 37-43	Example 24 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 56-58	All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or oxycodone hydrochloride solutions.
Col. 8, line 62	A stock suspension of ibuprofen is . . .
Col. 9, lines 22-24	Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen . . .
Col. 9, lines 45-47	In order to study the interaction between oxycodone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected.
Col. 10, lines 25 & 26	The synergistic interaction of oxycodone hydrochloride and ibuprofen . . .
Col. 10, lines 29-31	. . . the analgesic effect of oxycodone along is presented in the ordinate, and that of ibuprofen alone is on the abscissa.
Col. 10, lines 32-34	. . . exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1.
Col. 10, lines 35 & 36	. . . representing oxycodone and ibuprofen alone . . .
Col. 10, lines 36-38	. . . representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios.
Col. 11, lines 31-33	. . . straight line additivity hypothesis for oxycodone HCl and ibuprofen . . .
Col. 12, lines 52-54	. . . analgesic synergism is established for all combinations of oxycodone and ibuprofen.
Col. 12, lines 55 & 56	By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone . . .
Col. 12, lines 62 & 63	. . . it is predicted that oxycodone and ibuprofen would demonstrate analgesic potentiation . . .

Column/Lines	Text
Table 1	TABLE 1 ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS Oxycodone Ibuprofen Oxycodone Ibuprofen
Col. 13, lines 49-55	1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

In response to the Applicants previous argument regarding the "principle of operation" of Baker et al., the Examiner stated that "[t]he 'principle of operation' of the Baker reference is to combine NSAID's (e.g., ibuprofen) with opioids (e.g., oxycodone) in order to achieve improved pain relief as compared to separate administration of the active agents." (see page 9, lines 12-14 of the Office Action). Again, Applicants have been unable to find support for this statement within Baker et al., and they respectfully request the Examiner to indicate support for this statement if it exists.

As set forth above, Baker et al. is specifically directed to ibuprofen in combination with opioid analgesics. Baker et al. ignore all other NSAID's, except in a discussion of the prior art from which Baker et al. depart. Accordingly, Applicants resubmit their previous argument that modifying the formulation of Baker et al. in view of Penning et al. as proposed by the Examiner by substituting ibuprofen with celecoxib would result in a dosage form which is not directed to the principle of operation described in Baker et al. (i.e., the purported synergism of narcotic analgesics and ibuprofen).

It is respectfully submitted that the Baker reference teaches away from substituting ibuprofen with another NSAID (e.g., celecoxib), because of the unexpected synergy that it purports for the combination of ibuprofen with a narcotic analgesic. Furthermore, Applicants submit that the Examiner is improperly picking and choosing the celecoxib of Penning et al. with the oxycodone of Baker et al. to recreate the claims of the present application. One "...cannot pick and choose among the individual elements of assorted prior art references to recreate the

claimed invention." *SmithKline Diagnostics, Inc. v. Helena Laboratories Corporation*, 859 F.2d 878, 887 (Fed. Cir. 1988).

The Examiner further stated that "the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980)...". Applicants respectfully point out that in *In re Kerkhoven*, the court held that it would be obvious to combine two known detergents to form a third composition It is respectfully submitted that the holding of *In re Kerkhoven* is irrelevant because in *Kerkhoven*, unlike here, there is no indication that there was "teaching away" of the combination.

In view of the above arguments, it is respectfully requested that the 35 U.S.C. 103(a) rejection over Baker et al. and Penning et al. be removed.

C. **Rejection under 35 U.S.C. 103 (a) over Baker et al. and Penning et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)**

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al. and Penning et al. in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.) The Examiner stated that "it would have been obvious to one of ordinary skill in the art . . . to utilize sustained release carriers for oxycodone including the beads/layers as taught by the Oshlack and Oshlack et al. patents for use in the Baker compositions ...".

This rejection is respectfully traversed. It is respectfully submitted that the Oshlack references do not cure the deficiencies of the Baker reference in view of the Penning reference as set forth above.

In view of the above arguments, it is respectfully requested that the 35 U.S.C. 103(a) rejection over Baker et al., Penning et al., Oshlack et al. and Oshlack et al. be removed.

V. CONCLUSION

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

Respectfully submitted,

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